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ORIGINAL INVESTIGATIONS

Coronary Stent Thrombosis With Vorapaxar Versus Placebo

Results From the TRA 2°P-TIMI 50 Trial

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ABSTRACT

BACKGROUND Vorapaxar, a novel thrombin receptor antagonist, reduces cardiovascular death and recurrent thrombotic events when added to standard antiplatelet therapy in patients with stable atherosclerotic vascular disease.

OBJECTIVES The goal of this study was to test the hypothesis that treatment with vorapaxar reduces the rate of coronary stent thrombosis (ST) in stable patients with a history of coronary stenting.

METHODS TRA 2°P-TIMI 50 (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis In Myocardial Infarction 50) was a multinational, randomized, double-blind, placebo-controlled trial of vorapaxar in stable patients with prior myocardial infarction, peripheral arterial disease, or stroke. We evaluated the rates of definite ST as adjudicated by a central events committee using Academic Research Consortium (ARC) criteria.

RESULTS A total of 26,449 patients were randomized, with 14,042 (53%) having a history of a coronary stent implantation before randomization, and an additional 449 patients receiving a coronary stent during the trial (total 14,491). During follow-up (median 2.5 years), there were 152 definite ST events, with the majority (92%) occurring late or very late. Vorapaxar reduced ARC definite ST (1.1% vs. 1.4%, hazard ratio [HR]: 0.71, 95% confidence interval [CI]: 0.51 to 0.98; $p = 0.037$). The reduction was consistent, regardless of time from percutaneous coronary intervention, history of diabetes, use of drug-eluting stents, and use of dual antiplatelet therapy (DAPT) at randomization. Vorapaxar increased GUSTO moderate/severe bleeding (HR: 1.57, 95% CI: 1.26 to 1.94; $p < 0.001$).

CONCLUSIONS The rate of ARC definite ST in stable patients, the majority of whom were receiving DAPT, was approximately 1.4% at 3 years. In stable patients with coronary stenting receiving standard antiplatelet therapy, vorapaxar administered for long-term secondary prevention significantly reduced ARC definite ST, including very late ST. (Trial to Assess the Effects of Vorapaxar [SCH 530348; MK-5348] in Preventing Heart Attack and Stroke in Patients With Atherosclerosis [TRA 2°P-TIMI 50] [P04737]; NCT00526474) (J Am Coll Cardiol 2014;64:2309–17) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

ADP = adenosine diphosphate

ARC = Academic Research Consortium

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

FDA = U.S. Food and Drug Administration

HR = hazard ratio

MI = myocardial infarction

NNH = number needed to harm

NNT = number needed to treat

PAD = peripheral artery disease

PAR = protease-activated receptor

ST = stent thrombosis

TIA = transient ischemic attack

Stents are routinely used in coronary interventions to reduce the risk of complications such as acute dissection and recoil, as well as late coronary restenosis. Stent thrombosis (ST) is an uncommon, but serious, complication of coronary stenting, and may occur at various times after implantation. ST may be classified on the basis of timing as acute (<24 h), subacute (24 h to 30 days), late (30 days to 1 year), and very late (>1 year) (1–3). Late and very late ST occur at a lower rate than acute and subacute ST, but remain a life-threatening complication (4,5).

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Dual antiplatelet therapy with aspirin and an adenosine diphosphate (ADP) receptor blocker reduces ST compared with aspirin monotherapy. Newer generations of more potent ADP receptor blockers (e.g., prasugrel, ticagrelor) further reduce this risk relative to clopidogrel within the first year after an acute coronary syndrome (ACS) (6,7). It is unknown whether intensive antiplatelet therapy in patients with stable coronary artery disease and prior coronary stenting reduces later events, particularly very late ST. It is also not known whether antiplatelet agents targeting novel receptors and pathways are effective at modifying the risk of stent-related events.

The TRA 2°P-TIMI 50 trial (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis In Myocardial Infarction 50) studied vorapaxar, a novel antiplatelet agent acting through inhibition of the platelet protease-activated receptor (PAR)-1, for long-term secondary prevention when added to standard antiplatelet therapy, including aspirin (98%) and a thienopyridine (78%), in patients with stable atherosclerosis, including prior myocardial infarction (MI), prior stroke, and peripheral arterial disease (PAD) (8,9). We tested the hypothesis that PAR-1 inhibition with vorapaxar would reduce the risk of ST in stable patients in whom a coronary stent was implanted, and evaluated whether any effect observed was modified by background antiplatelet therapy or timing from stent implantation.

METHODS

STUDY POPULATION AND PROCEDURES. TRA 2°P-TIMI 50 was a multinational, randomized, double-blind, placebo-controlled trial among 26,449 subjects with stable atherosclerotic vascular disease manifested by prior MI, PAD, or ischemic stroke (8). The trial design details were previously reported (8,9). Participants in whom a coronary stent was implanted before randomization or who received a coronary stent during follow-up are the basis for the present, pre-specified analysis. For patients receiving a first coronary stent during follow-up, observation was started at the time of stent placement. Additional analyses of safety and efficacy using this pre-specified population with coronary stents, but excluding patients with history of stroke or transient ischemic attack (TIA), are presented in the Results section, consistent with the population approved for the use of vorapaxar by the U.S. Food and Drug Administration (FDA) (10).

Patients with MI qualified for the trial on the basis of a history of spontaneous MI occurring 2 weeks to 12 months before randomization (8). In order to qualify for inclusion on the basis of PAD, patients were required to have a history of intermittent claudication in conjunction with an ankle-brachial index <0.85 or previous revascularization for limb ischemia. Patients with qualifying stroke were required to have a history of symptomatic ischemic stroke occurring 2 weeks to 12 months before randomization. Patients were ineligible if they had a planned revascularization that

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had not yet been performed, had a history of a bleeding diathesis, a history of intracranial hemorrhage, or were receiving vitamin K antagonist therapy.

Details of prior coronary stenting were collected for all patients at baseline, and information for new coronary stents were collected during follow-up. The institutional review board or ethics committee for each participating institution approved the trial. All patients gave written informed consent.

Randomization was stratified both by qualifying disease state and by the pre-randomization assessment of whether use of a thienopyridine was planned (8). Eligible patients were randomized in a 1:1 fashion to receive vorapaxar 2.5 mg daily or matching placebo.

ENDPOINTS. The primary efficacy and safety definitions, as well as the results of the TRA 2°P-TIMI 50 trial were previously described (9). All potential ST events during the trial were collected through investigator report and prospective review of all cases of death, MI, urgent coronary revascularization, and unstable angina for possible unreported ST. Source documents, including hospitalization records and angiogram reports, were collected for all potential ST events and assembled into endpoint packets for review and formal adjudication by the clinical events committee (8).

To qualify as definite thrombosis in accordance with the Academic Research Consortium (ARC) (1), there needed to be an angiographic report documenting Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stented region in the presence of a thrombus, or TIMI flow grade 1, 2, or 3 and the presence of thrombus originating in the stent or in the segment 5 mm proximal or distal to the stented region and at least 1 of the following criteria: new onset of ischemic symptoms at rest (typical pain >20 min); new ischemic electrocardiographic changes suggestive of acute ischemia; typical rise and fall in cardiac biomarkers (1,9). Any unexplained death within 30 days of coronary stenting, or MI at any time occurring in the territory of an implanted stent without angiographic confirmation, or other obvious cause qualified as probable ST, and any unexplained death more than 30 days after coronary stenting qualified as possible ST, in accordance with the ARC criteria (9). Incidental angiographic documentation of silent stent occlusion in the absence of clinical signs or symptoms was not considered a confirmed ST (9).

STATISTICAL METHODS. Baseline characteristics were compared using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous ones. Efficacy analyses were performed using a Cox proportional hazards model, with the investigational treatment allocation and planned use of a thienopyridine as covariates. In addition, subgroups of interest were analyzed using the Cox model and including the subgroup, randomized treatment, and relevant interaction terms. Cumulative event rates at 3 years were calculated with the Kaplan-Meier method. Efficacy data were analyzed on an intention-to-treat basis. Analyses were performed using Stata version 12.1 (Stata Corp., College Station, Texas).

TABLE 1 Baseline Characteristics (Randomized Treatment Allocation)

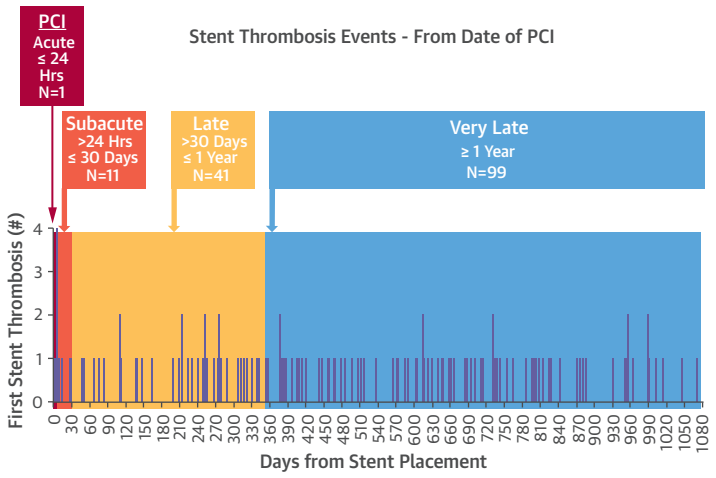
	Vorapaxar (n = 7,223)	Placebo (n = 7,268)	p Value
Demographics			
Age, yrs	59 (52-67)	59 (51-66)	0.31
Female	1,426 (20)	1,370 (19)	0.17
White race	6,551 (91)	6,548 (90)	0.19
Weight <60 kg	342 (5)	326 (5)	0.48
Clinical characteristics			
Diabetes mellitus	1,605 (22)	1,595 (22)	0.69
Hypertension	4,582 (63)	4,650 (64)	0.49
Hyperlipidemia	6,203 (86)	6,234 (86)	0.86
Current smoker	1,469 (20)	1,553 (21)	0.13
Peripheral artery disease	985 (14)	1,007 (14)	0.70
CrCl at baseline <60 ml/min	686 (10)	633 (9)	0.11
Coronary artery bypass grafting	649 (9)	690 (10)	0.29
Prior myocardial infarction	6,967 (97)	7,001 (96)	0.71
Prior STEMI	3,890 (57)	3,812 (56)	0.11
Drug-eluting stent	3,237 (46)	3,282 (47)	0.65
Baseline medical therapy			
Aspirin	7,072 (98)	7,134 (98)	0.28
Thienopyridine	6,147 (85)	6,141 (85)	0.31
Aspirin and thienopyridine therapy	6,011 (83)	6,028 (83)	0.65

Values are median (interquartile range) or n (%).
CrCl = creatinine clearance; STEMI = ST-segment elevation myocardial infarction.

RESULTS

BASELINE CHARACTERISTICS. A total of 14,491 patients had at least 1 coronary stent. Of these patients, 14,042 (97%) had a coronary stent before randomization, and 449 (3%) received a first coronary stent during follow-up. Just under one-half of patients (47%) had drug-eluting stents (DES). The median duration of follow-up was 2.5 years. The median time from most recent coronary stent implantation to randomization was 3 months. Baseline characteristics were balanced between treatment groups and are shown in Table 1. The majority of patients (93%) with coronary stents qualified for the trial with a recent MI, 22% were diabetic, 98%

FIGURE 1 Timing of Individual ST Events From Time of PCI



Overall, 1% of events were acute, 7% were subacute, 27% were late, and 65% were very late. Of the total, 92% of definite stent thrombosis (ST) events were late or very late. PCI = percutaneous coronary intervention.

received aspirin, and 83% received dual antiplatelet therapy (DAPT) with aspirin and a thienopyridine, predominantly clopidogrel. Use of other background cardiovascular therapies was frequent, including statins (95%) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (79%).

STENT THROMBOSIS. During follow-up there were 152 occurrences of ARC definite ST. The majority (92%) of events in this stable secondary prevention population occurred late or very late (>1 year) after stent implantation (**Figure 1**, Online Figure 1). Definite ST events occurring more than 1 year from stent implantation (65%) were distributed evenly over the follow-up period (**Figure 1**). The rate of ARC definite ST in the placebo group was 1.4% at 3 years (0.47% annualized). There were 169 patients with definite/probable ST (placebo event rate 0.50% annualized), and 310 patients with definite/probable/possible ST (placebo event rate of 0.90% annualized).

Compared with the 14,339 patients with coronary stents who did not develop definite ST, subjects who experienced a definite ST event (ARC definite) were younger, had a greater prevalence of dyslipidemia and current tobacco use, and more frequently had DES (61% vs. 46%; $p < 0.001$) (Online Table 1). There was no significant regional heterogeneity in the occurrence of definite ST ($p = 0.07$).

EFFECT OF PAR-1 INHIBITION WITH VORAPAXAR ON ST. Vorapaxar significantly reduced ARC definite ST compared with placebo by 29% (1.1% vs. 1.4%, hazard ratio [HR]: 0.71, 95% confidence interval [CI]: 0.51 to 0.98; $p = 0.037$) (**Table 2**, **Figure 2**). This reduction was directionally consistent in all subgroups, including prior ST-segment elevation MI, whether or not the patient had a DES, and smoking status (**Figure 3**). Patients with diabetes had a numerically greater reduction in definite ST with vorapaxar (0.60% vs. 1.57%, HR: 0.38, 95% CI: 0.17 to 0.85; $p = 0.019$) compared with nondiabetic patients (1.21% vs. 1.37%, HR: 0.81, 95% CI: 0.57 to 1.16; $p = 0.25$); however, there was no definite statistical heterogeneity (p for interaction = 0.092) (**Figure 3**). The reduction in definite ST was consistent when limiting the population to stented patients who qualified for the trial with MI or PAD and had no history of stroke or TIA (1.0% vs. 1.4%, HR: 0.70, 95% CI: 0.50 to 0.98; $p = 0.039$) (**Table 2**, Online Table 2, **Figure 3**). In addition, findings were numerically consistent, but no longer statistically significant, when using broader, less specific definitions of ST, including definite/probable ST (HR: 0.74, 95% CI: 0.55 to 1.01; $p = 0.058$) and definite/probable/possible ST (HR: 0.84, 95% CI: 0.67 to 1.05; $p = 0.12$) (**Table 2**).

TIMING OF ST. The reduction in definite ST with vorapaxar was consistent at all previously defined times, including events occurring within the first month, from 30 days to 1 year, and after 1 year (**Figure 4**). Very late ST was significantly reduced with vorapaxar (HR: 0.65, 95% CI: 0.43 to 0.97; $p = 0.037$).

OUTCOMES AFTER ST. Definite ST required documentation of ST, thereby excluding patients who died before angiography; however, 11% (16 of 152) died after a definite ST event, with the majority (11 of 16) dying within 4 days. Mortality after definite/probable ST was 14% (23 of 169), with the majority (13 of 23) occurring at the time of the event.

INFLUENCE OF BACKGROUND ANTIPLATELET THERAPY. The majority of patients were on background aspirin (98%) and, when stratified by aspirin dose (low dose ≤150 mg, high dose >150 mg), there was no heterogeneity in the reduction in definite ST with vorapaxar (high dose HR: 0.62, 95% CI: 0.34 to 1.13; low dose HR: 0.78, 95% CI: 0.53 to 1.15; p for interaction = 0.52) compared with placebo.

The majority (83%) of patients were on DAPT with aspirin and a thienopyridine (~98% clopidogrel) at baseline. The reduction in definite ST was similar in those planned for thienopyridine therapy (HR: 0.72, 95% CI: 0.51 to 1.02) and those not planned for thienopyridine therapy (HR: 0.67, 95% CI: 0.29 to 1.54) (p for interaction = 0.88) (**Figure 5**).

To determine whether the reduction in definite ST with vorapaxar was consistent in patients treated with long-term thienopyridine therapy, a sensitivity analysis was performed, evaluating the effect of vorapaxar in the subgroup of patients treated with thienopyridine, both at baseline and at 18 months or the end of follow-up (long-term thienopyridine: n = 6,779, 59% of those on DAPT at baseline). The reduction in definite ST with vorapaxar was consistent in patients on long-term thienopyridine therapy (HR: 0.72, 95% CI: 0.51 to 1.04), without heterogeneity from the effect of vorapaxar in patients who were on a thienopyridine at randomization, but stopped before 18 months (short-term thienopyridine 41%, HR: 0.87, 95% CI: 0.33 to 2.25; p for interaction = 0.73).

EFFICACY AND BLEEDING IN PATIENTS WITH CORONARY STENTS. Consistent with the primary findings in the overall trial, in the population with coronary stents, vorapaxar reduced the primary endpoint of cardiovascular death, MI, or stroke (HR: 0.83, 95% CI: 0.74 to 0.93; p = 0.001) (Table 2) with benefit driven primarily by reductions in MI (HR: 0.82, 95% CI: 0.72 to 0.94; p = 0.003) (Table 2) and ischemic stroke (HR: 0.68, 95% CI: 0.49 to 0.94; p = 0.02) (Table 2). GUSTO (Global Utilization Of Streptokinase and Tpa for Occluded arteries) moderate or severe bleeding was increased (HR: 1.57, 95% CI: 1.26 to 1.94) (Table 2). In this population with coronary stents, severe bleeding events, including intracranial hemorrhage (placebo rate 0.4% at 3 years, or 0.13% per year) and fatal bleeding (0.1% at 3 years or 0.03% per year) (Table 2), were infrequent. In this cohort, rates of intracranial hemorrhage and fatal bleeding were not statistically increased with vorapaxar (Table 2). When examined among patients in the FDA-approval population (MI or PAD and no history of stroke or TIA) who had coronary stents, findings with vorapaxar were similar, with a reduction in definite ST (HR: 0.70, 95% CI: 0.50 to 0.98; p = 0.039, number needed to treat [NNT] = 277) and cardiovascular death/MI/stroke (HR: 0.79, 95% CI: 0.70 to 0.89; p < 0.001, NNT = 56), but an increase in GUSTO moderate or severe bleeding (HR: 1.50, 95% CI: 1.20 to 1.89; p < 0.001, number needed to harm [NNH] = 112) (Table 2).

TABLE 2 Efficacy and Safety Endpoints

Endpoint	Vorapaxar	Placebo	Hazard Ratio (95% CI)	p Value
All patients with coronary stents	7,223	7,268		
Stent thrombosis				
Definite	63 (1.1)	89 (1.4)	0.71 (0.51–0.98)	0.037
Definite or probable	72 (1.2)	97 (1.5)	0.74 (0.55–1.01)	0.058
Definite, probable or possible	141 (2.2)	169 (2.7)	0.84 (0.67–1.05)	0.12
Major cardiovascular events				
CV death, MI, stroke	565 (9.1)	680 (10.7)	0.83 (0.74–0.93)	0.001
CV death	120 (1.9)	134 (2.2)	0.90 (0.71–1.16)	0.43
MI	423 (6.9)	515 (8.1)	0.82 (0.72–0.94)	0.003
Ischemic stroke	62 (1.1)	92 (1.5)	0.68 (0.49–0.94)	0.019
Bleeding				
ICH	34 (0.6)	23 (0.4)	1.51 (0.89–2.56)	0.13
Fatal bleed	12 (0.2)	8 (0.1)	1.53 (0.63–3.75)	0.35
GUSTO moderate	146 (2.6)	83 (1.4)	1.79 (1.37–2.35)	<0.001
GUSTO severe	70 (1.2)	58 (1.0)	1.23 (0.87–1.74)	0.25
GUSTO moderate or severe	209 (3.6)	136 (2.3)	1.57 (1.26–1.94)	<0.001

	Vorapaxar	Placebo	Hazard Ratio (95% CI)	p Value	NNT/NNH
Patients with coronary stents and no stroke or TIA (FDA-approval population)	6,813	6,846			
Stent thrombosis					
Definite	59 (1.1)	84 (1.4)	0.70 (0.50–0.98)	0.039	277
Definite or probable	66 (1.2)	91 (1.5)	0.73 (0.53–1.00)	0.049	
Definite, probable or possible	129 (2.2)	158 (2.7)	0.82 (0.65–1.04)	0.10	
Major cardiovascular events					
CV death, MI, stroke	479 (8.1)	604 (9.9)	0.79 (0.70–0.89)	<0.001	56
CV death	105 (1.8)	117 (2.1)	0.91 (0.70–1.18)	0.47	
MI	370 (6.3)	459 (7.6)	0.81 (0.70–0.93)	0.002	
Ischemic stroke	39 (0.7)	76 (1.3)	0.52 (0.35–0.76)	<0.001	
Bleeding					
ICH	27 (0.5)	22 (0.4)	1.25 (0.71–2.19)	0.44	1,334
Fatal bleed	10 (0.2)	6 (0.1)	1.69 (0.62–4.66)	0.31	1,691
GUSTO moderate	130 (2.4)	75 (1.3)	1.76 (1.33–2.34)	<0.001	
GUSTO severe	60 (1.1)	53 (0.9)	1.15 (0.79–1.66)	0.46	
GUSTO moderate or severe	185 (3.4)	125 (2.2)	1.50 (1.20–1.89)	<0.001	112

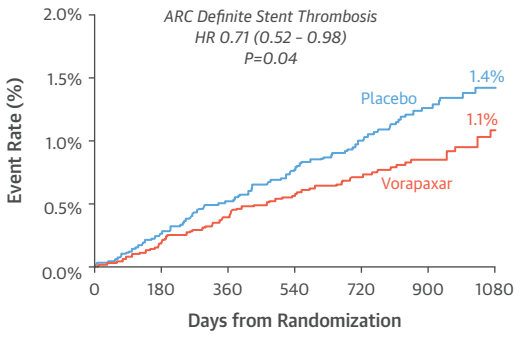
Values are n or n (%) except as indicated.

CI = confidence interval; CV = cardiovascular; FDA = U.S. Food and Drug Administration; GUSTO = Global Utilization Of Streptokinase and tPA for Occluded arteries; ICH = intracranial hemorrhage; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; TIA = transient ischemic attack.

DISCUSSION

In stable patients with established atherosclerosis and a history of coronary stenting, adding vorapaxar to standard background antiplatelet therapy for long-term secondary prevention of atherothrombotic events reduced definite ST (Central Illustration). This reduction was consistent, regardless of the dose of aspirin used or the use of a thienopyridine. Notably, vorapaxar reduced the incidence of very late ST (occurring more than a year after implantation) with consistent benefit at all time points from stent implantation. Together, these findings identify PAR-1 as a therapeutic target for reducing the risk of definite ST in long-term secondary prevention (Central Illustration). As anticipated, this potent antiplatelet drug increased bleeding. However, there was no increase in fatal or intracranial bleeding

FIGURE 2 Definite ST by Randomized Treatment



This figure shows ARC definite stent thrombosis (ST) events over 1,080 days (3 years) from randomization stratified by treatment allocation (vorapaxar in **salmon**, placebo in **blue**). ARC = Academic Research Consortium; HR = hazard ratio.

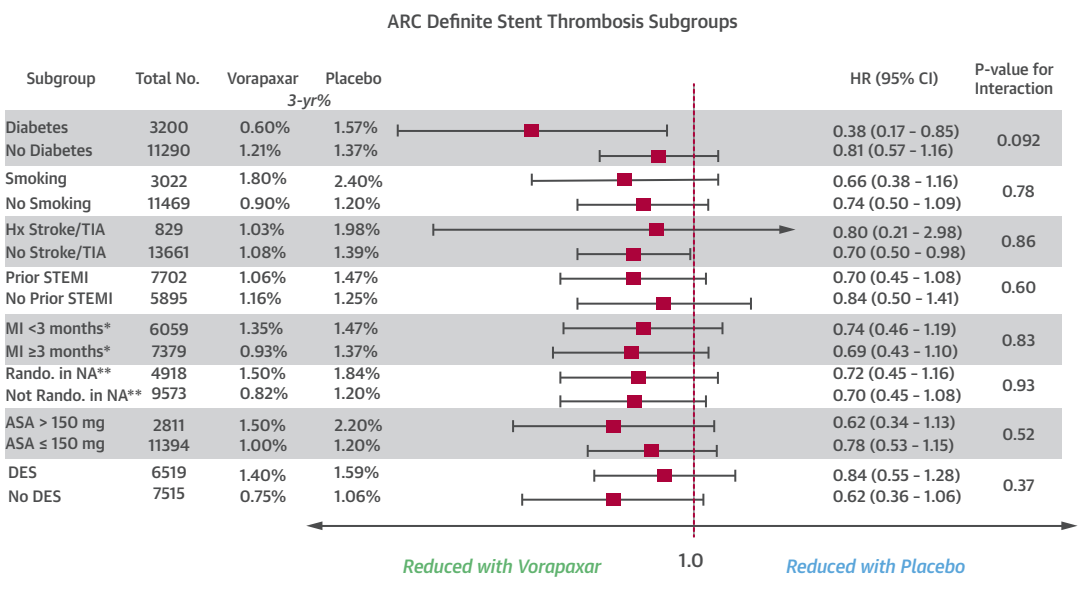
with vorapaxar in this population with coronary stents.

ANTIPLATELET THERAPY AND VERY LATE ST. The incidence of very late ST is not well established, with few robustly sized studies of patients with stable coronary artery disease and coronary stents receiving modern therapy. In a recent publication, the annualized rate of definite ST after ACS was 1.93% in patients with ACS within a year (7). A recently published meta-analysis, including patients receiving percutaneous coronary intervention for any indication (stable coronary artery disease and ACS), reported a composite 1.5% incidence of definite ST at 22 months (0.81% annualized) (11).

In this population of stable patients with prior MI, 98% on aspirin and 83% on DAPT, we observed an annual rate of definite ST of 0.47%. Of note, although the majority of patients had a history of MI in the last year, ST events continued to occur at a linear rate even a year after stent implantation, without any sign of decreasing frequency with time. Because of this constant risk, the stable nature of our cohort, and the 3 years of follow-up (placebo group in **Figure 2**), the majority of events (65%) accrued more than a year after stent implantation.

Although the absolute rate of definite ST is low relative to de novo MI, as we previously reported in the cohort who qualified with MI (2.7% per year), it is similar to that of ischemic stroke in the same population (1.5% at 3 years, 0.47% per year) (12). Similar to

FIGURE 3 Hazard of Definite ST by Subgroup



This figure shows the consistent reduction of ARC definite stent thrombosis with vorapaxar compared to placebo when examined by subgroups, including presence of diabetes mellitus, smoking stats, timing of most recent myocardial infarction (MI), aspirin (ASA) dose, and presence of a drug-eluting stent (DES). *Time from index myocardial infarction to randomization. **Randomized in North America versus randomized outside of North America. Hx = history; MI = myocardial infarction; NA = North America; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; other abbreviations as in **Figure 2**.

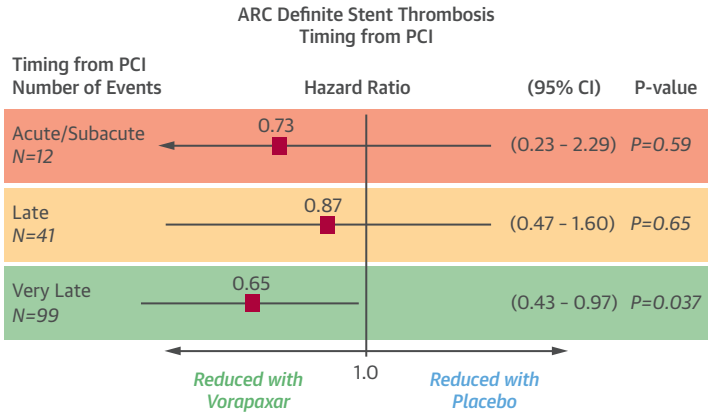
ischemic stroke, ST remains a feared ischemic outcome because of high rates of associated mortality. In a recent analysis from the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial, ST was associated with increased rates of all-cause mortality, with a similar pattern observed in the current cohort (7). This concern has been the impetus for a series of trials investigating whether prolonged DAPT with aspirin and a thienopyridine can modify the risk of late ischemic events (13).

Completed trials of prolonged DAPT beyond a year from stenting have not shown reduction of ischemic events or ST; however, these trials may have been underpowered for rare events (14,15). PAR-1 is expressed on a variety of cell types, including vascular smooth muscle and endothelium, and inhibition of PAR-1 in animals was shown to have antimitogenic effects in balloon-injured vessels. Vorapaxar was shown to reduce peripheral revascularization in a manner that suggests mechanisms beyond that of platelet inhibition alone (16). Whether the benefit of vorapaxar in reduction of definite ST is solely mediated by PAR-1 antagonism on platelets is uncertain and warrants further study.

Although this analysis was focused on the question of whether PAR-1 inhibition reduces coronary ST in stable patients with a history of stenting, data are presented regarding the broad efficacy and safety of vorapaxar in patients with coronary stents and no history or stroke or TIA (FDA-approval population). On the basis of the overall reduction in major adverse cardiovascular events (cardiovascular death, MI, or stroke), the NNT is 56 in the stented population. Because ST is infrequent in stable patients, the NNT for vorapaxar for this endpoint is 227. GUSTO moderate or severe bleeding was increased with an NNH of 112. There were numeric but not statistically significant increases in GUSTO severe bleeding (NNH = 939), intracranial hemorrhage (NNH = 1,334), and fatal bleeding (NNH = 1,691). It is not possible to comment on the magnitude of benefit of other antithrombotics (e.g., prasugrel or ticagrelor) in this population, as they have not yet been studied in this stable setting. Ongoing trials will provide such data in the future.

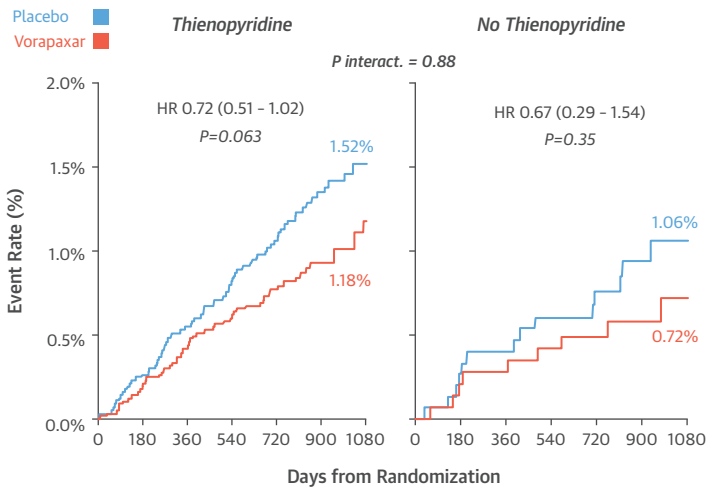
STUDY LIMITATIONS. First, the adjudication of ST in this study was performed using detailed medical records, including angiographic reports, rather than central review of the angiograms. Although use of central "core lab" angiographic review increases detection of ST, the process used in this study is consistent with that used in several recent analyses of ST (6,7,17). The impact would only be expected to diminish our power to detect a difference between therapies, and any loss of specificity would be expected to bias our analyses toward the null result. Secondly, because of this trial's timing, contemporary antiplatelet therapy after stenting was predominantly with clopidogrel. Although we have shown that PAR-1 antagonism with vorapaxar adds to ADP receptor

FIGURE 4 Consistent Reduction in ARC Definite ST With Vorapaxar by Timing of the Event



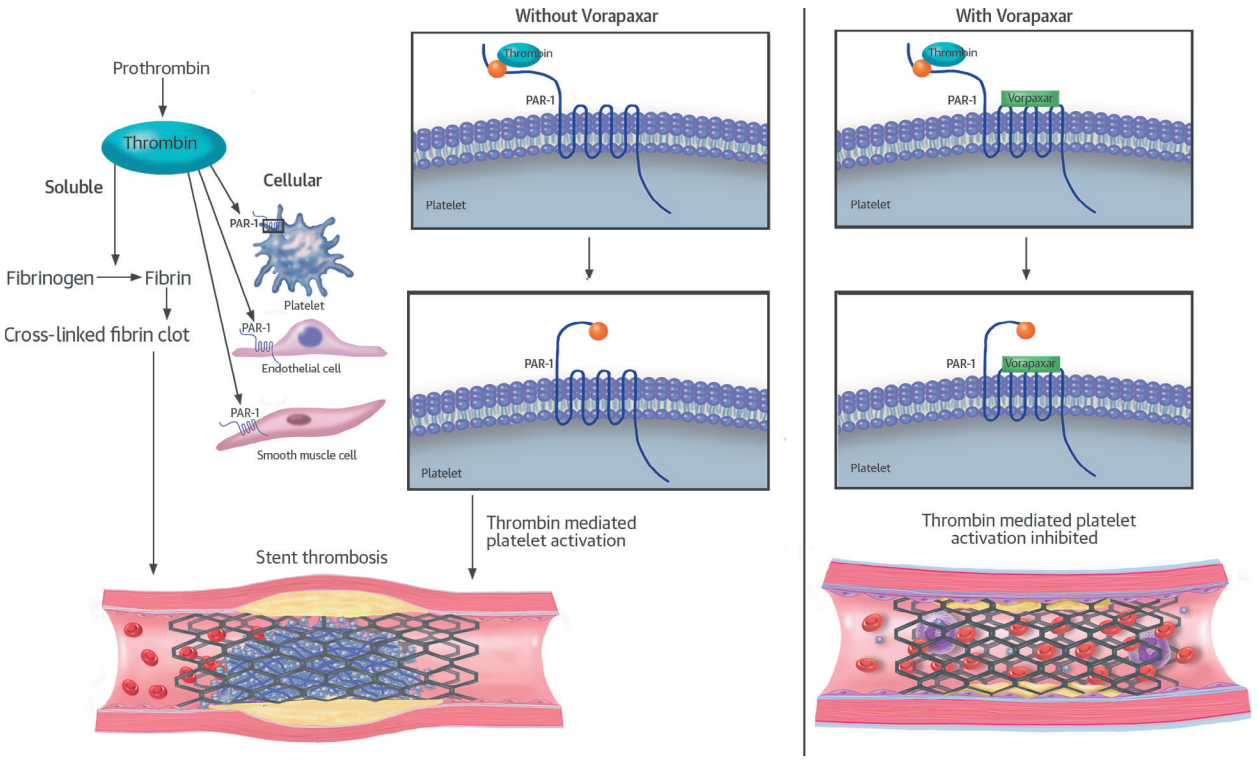
Stent thrombosis events are divided into acute/subacute (occurred in 12, or 0.08%, at 30 days, **orange**), late (occurred in 41, or 0.28%, from 30 days to 1 year, **yellow**), and very late (occurred in 99, or 0.68%, over an average of 2.5 years, **green**). CI = confidence interval; other abbreviations as in Figure 2.

FIGURE 5 ARC Definite Thrombosis Over 1,080 Days (3 Years) With Vorapaxar Versus Placebo



This figure shows the ARC definite thrombosis over 1,080 days (3 years) with vorapaxar **(salmon)** versus placebo **(blue)** stratified by background thienopyridine use. Abbreviations as in Figure 2.

CENTRAL ILLUSTRATION **The Role of PAR-1 in the Pathogenesis of Stent Thrombosis**



Bonaca, M.P. et al. J Am Coll Cardiol. 2014; 64(22):2309-17.

Thrombin activation of protease-activated receptor (PAR-1) and the pathogenesis of stent thrombosis. Vorapaxar is a PAR-1 antagonist, which blocks thrombin mediated platelet activation and reduces stent thrombosis.

pathway inhibition, we do not have data to address this question in the setting of more potent inhibition with prasugrel or ticagrelor. In addition, although specific DES types are not available, the types represented may include those used during and prior to 2007, when the trial completed recruitment. Therefore, findings, particularly regarding absolute rates of ST, should not be extrapolated to later-generation stent types. Thirdly, despite this study's large sample size, given the low overall incidence of late and very late ST, our statistical power to identify heterogeneity in some subgroup analyses is low. Fourthly, the effect of vorapaxar on broader, less specific ST endpoints was numerically consistent with that observed for definite ST, but no longer statistically significant. Definite ST is the most specific of the ARC endpoints, and is therefore most likely to represent the true effect of therapy on ST. Broader definitions, such as probable ST and possible ST, include events such as unexplained death, which may or may not be related to ST, and thus, although they increase the total number of events, they decrease the specificity of the endpoint for true ST. Lastly, although the findings may appear to contrast with those from the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) trial, in which ST was not significantly reduced, updated analyses from this trial using angiographic adjudication have shown a consistent reduction with vorapaxar, further supporting the findings of this analysis (18).

Any clinical use of vorapaxar would have to weigh the observed reduction in ST and other thrombotic events (9) against the risk of bleeding. Nevertheless, our findings provide important evidence for PAR-1 antagonism as a viable target for reducing late and very late ST, and indicate that a reduction in definite ST is an antithrombotic benefit of vorapaxar to be considered in weighing its potential benefits versus risks for the individual patient.

CONCLUSIONS

In stable patients with established atherosclerosis and a history of coronary stenting, long-term therapy with vorapaxar reduced the risk of definite ST. The benefit was consistent over time, including a reduction in very late events, occurring more than a year after stent implantation, and was not modified by background use of DAPT with aspirin and a thienopyridine.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In stable patients with coronary stents, the PAR-1 receptor antagonist vorapaxar reduced the risk of stent thrombosis by approximately 30% compared with placebo when added to aspirin or dual anti-platelet therapy with aspirin and a thienopyridine.

TRANSLATIONAL OUTLOOK: Further studies are needed to more accurately identify patients most likely to benefit from long-term therapy with vorapaxar and determine whether efficacy would be diminished or safety enhanced if aspirin were withdrawn from the combination regimen.

REFERENCES

1. Mauri L, Hsieh WH, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9.

2. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.

3. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.

4. Bavry AA, Kumbhani DJ, Helton TJ, et al. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med 2006;119:1056–61.

5. James SK, Stenestrand U, Lindback J, et al., SCAAR Study Group. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. N Engl J Med 2009;360:1933–45.

6. Wiviott SD, Braunwald E, McCabe CH, et al., TRITON-TIMI 38 Investigators. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet 2008;371:1353–63.

7. Steg PG, Harrington RA, Emanuelsson H, et al., PLATO Study Group. Stent thrombosis with ticagrelor versus clopidogrel in patients with acute coronary syndromes: an analysis from the prospective, randomized PLATO trial. Circulation 2013;128:1055–65.

8. Morrow DA, Scirica BM, Fox KA, et al., TRA 2°P-TIMI 50 Investigators. Evaluation of a novel antiplatelet agent for secondary prevention in patients with a history of atherosclerotic disease: design and rationale for the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P)-TIMI 50 trial. Am Heart J 2009;158:335–41.e3.

9. Morrow DA, Braunwald E, Bonaca MP, et al., TRA 2°P-TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 2012;366:1404–13.

10. ZONTIVITY (TM) oral tablets, vorapaxar oral tablets [product information]. Whitehouse Station, NJ: Merck & Co., Inc., 2014.

11. D'Ascenzo F, Bollati M, Clementi F, et al. Incidence and predictors of coronary stent thrombosis: evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses. Int J Cardiol 2013;167:575–84.

12. Scirica BM, Bonaca MP, Braunwald E, et al., TRA 2°P-TIMI 50 Steering Committee Investigators. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. Lancet 2012;380:1317–24.

13. Mauri L, Kereiakes DJ, Normand SL, et al. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. Am Heart J 2010;160:1035–41, 1041.e1.

14. Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med 2010;362:1374–82.

15. Valgimigli M, Campo G, Monti M, et al., Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012;125:2015–26.

16. Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2°P-TIMI 50. Circulation 2013;127:1522–9, 1529e1–6.

17. Mehta SR, Tanguay JF, Eikelboom JW, et al., CURRENT-OASIS 7 trial investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet 2010;376:1233–43.

18. Gibson CM, Tricoci P, Abueg C, et al. Lack of concordance between angiographic core laboratory and CEC in the assessment of stent thrombosis: results from the TRACER angiographic substudy. Eur Heart J 2013;34 Suppl 1:240.

KEY WORDS antiplatelet therapy, atherothrombosis, DES, PAR-1, stent, thienopyridine

APPENDIX For a supplemental figure and tables, please see the online version of this article.